UNITED STATES AIR FORCE
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Relating Blood Concentration Time Courses To Cardiac Sensitization Thresholds During Inhalation Of Halon Replacement Chemicals

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This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

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13. ABSTRACT (Maximum 200 words)

Human exposure to Halon and Halon replacement chemicals is often regulated on the basis of cardiac sensitization potential. The test results are evaluated in terms of a dose-response curve from which No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL) values are determined. This approach alone does not provide the information necessary to evaluate the cardiac sensitization potential for the chemical of interest under a variety of exposure concentrations and durations. In order to provide a tool for decision makers and regulators tasked with setting exposure guidelines for Halon replacement chemicals, a quantitative approach was established with allowed exposures to be assessed in terms of the chemical concentration in blood during the exposure. A Physiologically Based Pharmacokinetic (PBPK) model was used to simulate blood concentrations of Halon 1301, FC-3-1-10 (perfluorobutane, C_4F_{10}), HCFC-124 (chlorotetrafluoroethane, $CHClFCF_3$) HFC-125 (pentafluoroethane, CHF_2CF_3), HFC-227ea (heptafluoropropane, CF_3CHFCF_3), HFC-23 (trifluoromethane, CHF_3), HCFC-22 (chlorodifluoromethane, $CHClF_2$), HCFC-123 (dichlorotrifluoroethane, $CHCL_2CF_3$) and CF_3I (trifluoroiodomethane) during an inhalation exposure. The inhalation exposure time required to achieve the chemical blood level achieved in the LOAEL cardiac sensitization exposure was calculated for the Halon replacement chemicals. This work demonstrates a quantitative approach for use as a tool in establishing appropriate egress times for people exposed to inhalation of Halon replacement chemicals.

14. SUBJECT TERMS
Halon   Physiologically based pharmacokinetic (PBPK) model
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INTRODUCTION

Cardiac sensitization potential is a characteristic often used to determine the human health risk associated with exposure to halogenated hydrocarbons. Of particular interest are the halogenated hydrocarbons proposed as replacements for Halon 1301 in occupied space fire fighting applications. Most of the currently proposed Halon 1301 replacements are at least partially halogenated and potentially have cardiac sensitization potential at some exposure concentration.

Cardiac sensitization tests are conducted in dogs which are exposed to the chemical of interest in combination with an epinephrine challenge. In such tests, the animals are exposed via inhalation to the chemical for five minutes. Then the animals are challenged with epinephrine and monitored while the exposure continues for an additional five minutes. During the exposure period the cardiac electrical activity in each animal is monitored for cardiac arrhythmias. After a range of chemical concentrations has been evaluated using the cardiac sensitization protocol, the dose-response relationship can be used to establish the No Observed Adverse Effect Level (NOAEL) and Low Observed Adverse Effect Level (LOAEL).

The quantitative relationship between exposure at the LOAEL and the resulting concentration of chemical in blood can be used to make scientifically based decisions about the egress time for people occupying a facility at the time of chemical agent discharge. This approach involves evaluating the chemical concentration in blood that is achieved after five minutes of inhalation at the chemical LOAEL. The five minute inhalation time is a consequence of a standard cardiac sensitization protocol used in toxicity testing and represents the blood level likely to be achieved at the time the epinephrine challenge is presented in the testing procedure. The approach described in this work more closely aligns the currently accepted cardiac sensitization testing procedure with the human exposure scenarios subject to regulatory activity.

The quantitative link between the exposure concentration and blood levels of chemical achieved following inhalation of the chemicals is provided by a physiologically based pharmacokinetic model (PBPK). The PBPK model is a mathematical description of the uptake, distribution, metabolism and elimination of a chemical in the species of interest. The physiological compartments that compose the model are based on appropriate physiological and anatomical properties for the species as well as the chemical specific properties of the test compound. The use of PBPK models for kinetic description of chemical interaction with biological systems has been well represented in the scientific literature over the last decade (Andersen, 1981, Conolly and Andersen, 1991, Leung, 1991 and Ramsey and Andersen, 1984). Additionally, PBPK modeling approaches have been instrumental in activities requiring the extrapolation of kinetic or biochemical data between species (Clewell and Andersen, 1985). Given the extensive publication of PBPK model papers in peer-reviewed journals and the wide-spread use of these models in risk assessment activities, the merit of PBPK models is not the focus of this work. Rather, the focus of this work is to apply a PBPK approach to better define the chemical exposure time and conditions required to reach target levels of chemical in blood for the following set of proposed Halon 1301 replacement chemicals: FC-3-1-10 (perfluorobutane, C_4F_{10}), HCFC-124 (chlorotetrafluoroethane, $CHClFCF_3$), HFC-125 (pentafluoroethane,

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CHF$_2$CF$_3$), HFC-227ea (heptafluoropropane, CF$_3$CHFCF$_3$), HBFC22B1 (bromodifluoromethane, CHF$_2$Br), HFC-23 (trifluoromethane, CHF$_3$), HCFC-22 (chlorodifluoromethane, CHClF$_2$), HCFC-123 (dichlorotrifluoroethane, CHCl$_2$CF$_3$) and CF$_3$I (trifluoroiodomethane).

METHODS

Target Levels of Chemical in Blood

The target levels of chemical in blood were established by exercising a PBPK human model to simulate a 5 minute inhalation exposure to a LOAEL concentration of the test chemical. The blood level achieved five minutes into the LOAEL inhalation exposure was determined to be the target chemical concentration in blood and was subsequently used as the blood level at which cardiac sensitization was likely to occur. Once a target level of chemical in blood was established, the exposure time required to produce the target level was estimated. This procedure was conducted for humans under both rest and moderate (35-50 Watt) activity levels.

Physiologically Based Pharmacokinetic (PBPK) Model

The PBPK model used in this work was a modification of the model presented by Vinegar et al., 1994. The model was composed of physiological compartments for the liver, fat, lung, gut, slowly perfused and rapidly perfused tissues. The tissue blood flows and ventilation rates for humans under rest and exercise conditions were obtained from work published by Dankovic and Bailer, 1993, and are shown in Table 1.

Chemical Specific Model Parameters and Values

The available chemical specific data ranged considerably in terms of quantity and quality. In some cases human tissue partition coefficient data were available and in others only rodent data were available. For three of the chemicals, no partition coefficient data were available and the necessary partition coefficients were generated in our laboratory as part of this exercise. Many of the chemicals had gross rodent metabolism rate constant data, but none of them had human metabolism data. The assumption made for this work is that rat metabolism data can be extrapolated to humans using weight relationships. This assumption should not dramatically impact the work here as this group of chemicals shows as a general characteristic extremely low metabolic activity. This is particularly true for the highly fluorinated chemicals in the group. Since there is considerable diversity in the data used in this work, the chemical specific model parameters and values will be presented as a separate set for each chemical.

General Model Parameters and Values

Table 1. General Model Parameters and Values

Parameter	Resting	Moderate Activity
Gut Blood Flow *	0.2192	0.2093
Liver Blood Flow*	0.0885	0.0602
Fat Blood Flow*	0.0288	0.0400
Rapid Perfused Blood Flow*	0.4616	0.3188
Slowly Perfused Blood Flow*	0.2019	0.4319
Volume Fat **	0.215	0.215
Volume Gut**	0.022	0.022
Volume Liver**	0.027	0.027
Volume Rapid Perfused**	0.041	0.041
Volume Slowly Perfused**	0.575	0.575
Ventilation ***	17.4	43.1
Cardiac Output***	12.9	20.7
Body Weight (Kg)	70.0	70.0

* The values are given as the proportion of cardiac output.

** The values are given as the proportion of body weight.

*** The values are given as Liters/Hour/Kg body weight.

Trifluorobromomethane, Halon 1301

Human blood to air partition coefficients were conducted using a modification of the vial equilibration method of Gargas et al., 1989. The tissue to air partition coefficients were conducted in rat tissues. The metabolic rate constants were determined using gas uptake methods in Fischer-344 rats.

Table 2. Halon 1301 Parameter Values.

Parameter	Value
Molecular Weight (g/mole)	148.91
Blood:air Partition Coefficient (human)	0.34
Blood:air Partition Coefficient (rat)	0.72
Vmaxc*	0.00
Liver:air Partition Coefficient	0.85
Gut:air Partition Coefficient	0.69
Fat:air Partition Coefficient	3.95
Rapidly Perfused:air Partition Coefficient	0.85
Slowly Perfused:air Partition Coefficient	0.59

* Maximum Metabolism Rate per Kg body weight (mg/hr/Kg).

Trifluoroiodomethane, CF₃I

Human blood to air partition coefficients were conducted using a modification of the vial equilibration method of Gargas et al., 1989. The tissue to air partition coefficients were conducted in rat tissues. The metabolic rate constants were determined using gas uptake methods in Fischer-344 rats.

Table 3. CF₃I Parameter Values.

Parameter	Value
Molecular Weight (g/mole)	195.9
Blood:air Partition Coefficient (human)	0.97
Blood:air Partition Coefficient (rat)	1.75
Vmaxc*	0.375
Km, Affinity Constant (mg/L)	0.10
Liver:air Partition Coefficient	1.22
Gut:air Partition Coefficient	1.57
Fat:air Partition Coefficient	11.24
Rapidly Perfused:air Partition Coefficient	1.22
Slowly Perfused:air Partition Coefficient	1.27

* Maximum Metabolism Rate per Kg body weight (mg/hr/Kg).

Heptafluoropropane, HFC-227ea

Rat blood to air partition coefficients were conducted using a modification of the vial equilibration method of Gargas et al., 1989. The human blood:air partition coefficient used was one half the value of the rat blood:air partition coefficient. This is based on experience with CF₃I and Halon 1301. The tissue to air partition coefficients were conducted in rat tissues. The metabolic rate constants were determined using gas uptake methods in Fischer-344 rats.

Table 4. HFC-227ea Parameter Values.

Parameter	Value
Molecular Weight (g/mole)	170.0
Blood:air Partition Coefficient	0.225
Vmaxc*	0.00
Liver:air Partition Coefficient	0.42
Gut:air Partition Coefficient	0.45
Fat:air Partition Coefficient	1.58
Rapidly Perfused:air Partition Coefficient	0.42
Slowly Perfused:air Partition Coefficient	0.36

* Maximum Metabolism Rate per Kg body weight (mg/hr/Kg).

Pentafluorethane, HFC-125

Rat blood to air partition coefficients were conducted using a modification of the vial equilibration method of Gargas et al., 1989. The human blood:air partition coefficient used was one half the value of the rat blood:air partition coefficient. This is based on experience with CF_3I and Halon 1301. The tissue to air partition coefficients were conducted in rat tissues. The metabolic rate constants were determined using gas uptake methods in Fischer-344 rats.

Table 5. HFC-125 Parameter Values.

Parameter	Value
Molecular Weight (g/mole)	120.0
Blood:air Partition Coefficient	0.115
Vmaxc*	0.00
Liver:air Partition Coefficient	0.26
Gut:air Partition Coefficient	0.37
Fat:air Partition Coefficient	0.45
Rapidly Perfused:air Partition Coefficient	0.26
Slowly Perfused:air Partition Coefficient	0.34

* Maximum Metabolism Rate per Kg body weight (mg/hr/Kg).

Chlorotetrafluoroethane, HCFC-124

No human or rat partition coefficient values were available for HCFC-124 so the values for the structurally similar HCFC-142b were used as surrogates. Metabolic constants for HCFC-124 were determined using gas uptake techniques.

Table 6. HCFC-124 Parameter Values.

Parameter	Value
Molecular Weight (g/mole)	136.5
Blood:air Partition Coefficient	0.605
Vmaxc*	0.21
Km, affinity constant (mg/L)	0.30
Liver:air Partition Coefficient	1.48
Gut:air Partition Coefficient	1.48
Fat:air Partition Coefficient	17.43
Rapidly Perfused:air Partition Coefficient	1.48
Slowly Perfused:air Partition Coefficient	0.65

* Maximum Metabolism Rate per Kg body weight (mg/hr/Kg).

Dichlorotrifluoroethane, HCFC-123

Partition coefficient values were obtained using human tissue by using a modification of the vial equilibration method published by Gargas et al., 1989. The metabolic constants were derived in Fischer-344 rats via a gas uptake method.

Table 7. HCFC-123 Parameter Values.

Parameter	Value
Molecular Weight (g/mole)	152.93
Blood:air Partition Coefficient	1.90
Vmaxc*	8.80
Km, affinity constant (mg/L)	0.70
Liver:air Partition Coefficient	3.00
Gut:air Partition Coefficient	1.60
Fat:air Partition Coefficient	49.00
Rapidly Perfused:air Partition Coefficient	3.00
Slowly Perfused:air Partition Coefficient	3.00

* Maximum Metabolism Rate per Kg body weight (mg/hr/Kg).

Perfluorobutane, FC-3-1-10

Perfluorobutane partition coefficient values for rat blood, liver, muscle and fat and human blood were determined as part of this work. The method was a modification of the vial equilibration method as published by Gargas et al., 1989. The metabolic constants were assumed to be zero based on perfluorobutane's structural similarity to other fluorinated carbons evaluated as potential Halon replacement chemicals.

Table 8. FC3-1-10 Parameter Values.

Parameter	Value
Molecular Weight (g/mole)	237.98
Blood:air Partition Coefficient (Human)	0.45
Blood:air Partition Coefficient (Rat)	0.83
Vmaxc*	0.00
Liver:air Partition Coefficient	1.13
Gut:air Partition Coefficient	1.13
Fat:air Partition Coefficient	0.93
Rapidly Perfused:air Partition Coefficient	1.13
Slowly Perfused:air Partition Coefficient	1.22

* Maximum Metabolism Rate per Kg body weight (mg/hr/Kg).

Chlorodifluoromethane, HFC-22

Chlorodifluoromethane partition coefficient values for rat blood, liver, muscle and fat and human blood were determined as part of this work. The method was a modification of the vial equilibration method as published by Gargas et al., 1989. The metabolic constants were assumed to be zero based on structural similarity to other fluorinated carbons evaluated as potential Halon replacement chemicals. No reliable metabolic data was available for use in the simulation.

Table 9. HFC-22 Parameter Values.

Parameter	Value
Molecular Weight (g/mole)	86.45
Blood:air Partition Coefficient (Human)	0.52
Blood:air Partition Coefficient (Rat)	1.72
Vmaxc*	0.00
Liver:air Partition Coefficient	0.96
Gut:air Partition Coefficient	0.96
Fat:air Partition Coefficient	8.67
Rapidly Perfused:air Partition Coefficient	0.96
Slowly Perfused:air Partition Coefficient	1.18

* Maximum Metabolism Rate per Kg body weight (mg/hr/Kg).

Bromodifluoromethane, HBFC22B1

No partition coefficient or metabolism data were available for HBFC22B1, but because HBFC22B1 differs by only one fluorine atom from Halon 1301, the Halon 1301 partition coefficients and metabolic constants were used.

RESULTS

The relationship between inhalation time and chemical blood levels achieved was used to apply cardiac sensitization data to practical applications. A physiologically based pharmacokinetic model was used to estimate the blood levels that would be achieved in humans under resting and moderate activity level conditions when challenged with inhalation of Halon replacement chemicals. The times required for the chemical concentration in blood to reach the blood level obtained in the LOAEL exposures conducted in the cardiac sensitization tests were estimated and are presented in tables 10-12.

It should be noted that the chemical concentration in blood has not reached its steady-state value after five minutes of exposure. However, since a five minute period of chemical inhalation is used as the dosing step in the cardiac sensitization test conducted using a widely accepted protocol, the blood levels at the five minute point were used in this exercise. A representative time course of chemical in the blood during inhalation is shown in Figure 1.
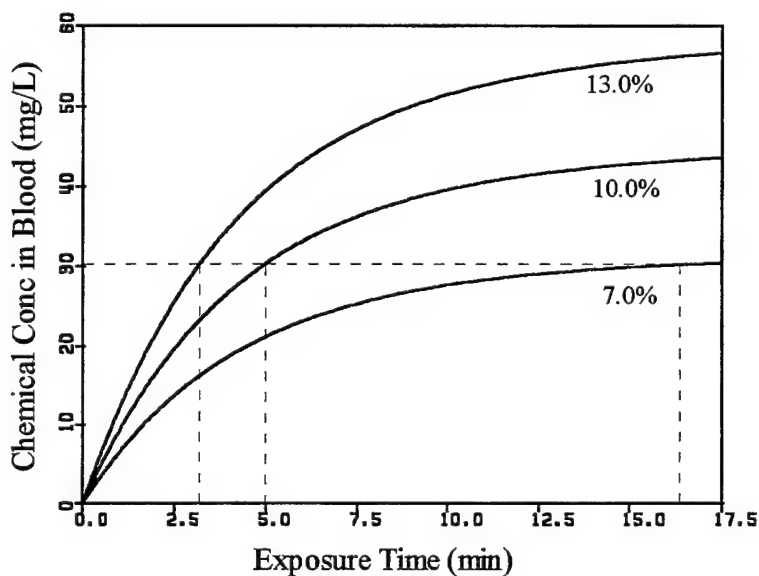

Figure 1.   Chemical Concentration in Blood During Inhalation of Halon Replacement. The percentages shown are the exposure concentrations. The LOAEL for this chemical is 10%.

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In the example shown in Figure 1, the five minute exposure to the LOAEL of the chemical gives the target chemical concentration in the blood of approximately 30 mg/L. The time required to reach the target chemical concentration in blood for exposure levels less than and greater than the LOAEL are shown as intersection points of the dashed lines and the x-axis.

Table 10. Exposure Time Required to Achieve LOAEL (Cardiac Sensitization) Blood Level [++]

Exposure Conc (% v/v)	HFC-125 ME/ R	HCFC-22 ME/ R	HFC-227ea ME/ R	Halon 1301[a] ME/ R	Halon 1301[b] ME/ R
3.0	*/ *	34.1/ 115.9	*/ *	*/ *	*/ *
4.0	*/ *	9.7/ 9.0	*/ *	47.6/ 142.2	*/ *
5.0	101.5/ *	5.0/ 5.0	*/ *	14.8/ 15.1	*/ *
6.0	30.9/ 115.3	3.5/ 3.6	93.6/ *	8.1/ 7.8	*/ *
7.0	14.5/ 16.9	2.8/ 2.9	22.3/ 61.3	5.7/ 5.7	*/ *
7.5	10.7/ 11.0	2.3/ 2.4	15.9/ 29.2	5.0/ 5.0	292.8/ *
8.0	8.6/ 8.6	2.0/ 2.0	11.9/ 13.7	4.5/ 4.5	47.6/ 142.2
9.0	6.3/ 6.3	1.7/ 1.8	7.6/ 7.5	3.7/ 3.8	23.7/ 42.0
10.0	5.0/ 5.0	1.7/ 1.8	5.6/ 5.6	3.2/ 3.2	14.9/ 15.1
10.5	4.6/ 4.6	n/a	5.0/ 5.0	3.0/ 3.1	12.3/ 11.8
11	4.2/ 4.2	1.6/ 1.6	4.5/ 4.5	2.8/ 2.9	10.4/ 10.0
12	3.6/ 3.6	1.4/ 1.4	3.8/ 3.8	2.5/ 2.6	8.1/ 7.8
13	3.2/ 3.2	1.3/ 1.3	3.3/ 3.4	2.3/ 2.3	6.6/ 6.6
14	2.9/ 2.9	1.2/ 1.2	3.0/ 3.0	2.1/ 2.1	5.7/ 5.6
15	2.6/ 2.6	1.1/ 1.1	2.7/ 2.7	1.9/ 1.9	5.0/ 5.0
16	2.4/ 2.4	1.0/ 1.0	2.5/ 2.5	1.8/ 1.8	4.5/ 4.5
17	2.2/ 2.2	<1 min/ <1 min	2.3/ 2.3	1.7/ 1.7	4.1/ 4.1
18	2.1/ 2.0	<1 min/ <1 min	2.1/ 2.1	1.6/ 1.6	3.7/ 3.8
19	2.0/ 1.9	<1 min/ <1 min	2.0/ 1.9	1.5/ 1.5	3.5/ 3.5
20	1.8/ 1.8	<1 min/ <1 min	1.8/1.8	1.4/ 1.4	3.2/ 3.2

[++]: All times in table are minutes required to reach the target chemical concentration in blood.

[a]: cardiac sensitization LOAEL is 7.5% v/v.

[b]: cardiac sensitization LOAEL is 15% v/v.

*: LOAEL blood level cannot be achieved during any length of exposure.

n/a: No evaluation was done at that exposure concentration. This allowed for multiple chemicals to be presented in the table.

R: Resting Human

ME: Human involved in moderate exercise (35-50W).

Table 11. Exposure Time Required to Achieve LOAEL (Cardiac Sensitization Blood Level[++]

Exposure Conc (% v/v)	HCFC-124 ME/ R	HCFC-123 ME/ R	HBFC-22B1 ME/ R	CF₃I ME/ R
0.2	*/ *	*/ *	*/ *	*/ *
0.4	*/ *	*/ *	*/ *	*5.0/ 5.0*
0.5	*/ *	*/ *	*/ *	n/a
0.6	*/ *	*/ *	*/ *	2.3/ 2.4
0.8	*/ *	*/ *	*/ *	1.6/ 1.6
1.0	*/ *	42.0/ 116.1	*/ *	1.2/ 1.2
1.5	n/a	10.7/ 10.2	n/a	n/a
2.0	7.5/ 7.4	*5.0/ 5.0*	76.4/ 412.2	0.55/ 0.55
2.5	*5.0/ 5.0*	3.3/ 3.5	17.6/ 20.6	n/a
3.0	3.8/ 3.8	2.5/ 2.7	9.0/ 8.6	0.36/ 0.36
3.9	2.7/ 2.7	n/a	*5.0/ 5.0*	n/a
4.0	2.6/ 2.6	1.7/ 1.9	4.8/ 4.8	0.26/ 0.26
5.0	2.0/ 2.0	1.3/ 1.5	3.4/ 3.4	0.21/ 0.21
6.0	1.6/ 1.6	1.1/ 1.2	2.7/ 2.7	0.17/ 0.17
7.0	1.4/ 1.4	0.9/ 1.0	2.2/ 2.2	0.15/ 0.15
8.0	1.2/ 1.2	<1 min/ <1 min	1.9/ 1.9	0.13/ 0.13
9.0	1.1/ 1.0	<1 min/ <1 min	1.7/ 1.6	<0.13 min/ <0.13 min
10.0	1.0/ 0.9	<1 min/ <1 min	1.5/ 1.5	<0.13 min/ <0.13 min
11.0	<1 min/ <1 min	<1 min/ <1 min	1.3/ 1.3	<0.13 min/ <0.13 min
12.0	<1 min/ <1 min	<1 min/ <1 min	1.2/ 1.2	<0.13 min/ <0.13 min
13.0	<1 min/ <1 min	<1 min/ <1 min	1.1/ 1.1	<0.13 min/ <0.13 min
14.0	<1 min/ <1 min	<1 min/ <1 min	1.0/ 1.0	<0.13 min/ <0.13 min

[++]: All times in table are minutes required to reach the target chemical concentration in blood.

* : LOAEL blood level cannot be achieved during any length of exposure.

n/a: No evaluation was done at that exposure concentration. This allowed for multiple chemicals to be presented in the same table.

R: Resting Human

ME: Human involved in moderate exercise (35-50W).

Table 12. Exposure Time Required to Achieve LOAEL (Cardiac Sensitization Blood Level[++]

Exposure Conc (% v/v)	FC3-1-10 ME/ R
15	*/ *
20	49.8/ 165.1
25	18.5/ 19.1
30	9.4/ 8.9
35	6.4/ 6.3
40	5.0/ 5.0
45	4.1/ 4.2
50	3.5/ 3.6
55	3.1/ 3.1
60	2.8/ 2.8
65	2.5/ 2.5
70	2.3/ 2.3
75	2.1/ 2.1
80	2.0/ 2.0

[++]: All times in table are minutes required to reach the target chemical concentration in blood.

* : LOAEL blood level cannot be achieved during any length of exposure.

R: Resting Human

ME: Human involved in moderate exercise (35-50W).

No evaluation of HFC-23 was made due to the lack of partition coefficient and metabolism data. We attempted to measure human blood:air partition coefficients for HFC-23 using the vial equilibration method used for the other chemicals of interest. However, the resulting value was essentially zero by the method used and could not be used in the physiologically based pharmacokinetic model. HFC-23 shows very low acute toxicity and was reported as not cardiotoxic to dogs at 800000 ppm.

Blend A was evaluated based on its halogenated components: HCFC-22 (82%), HCFC-124 (9.5%) and HCFC-123 (4.75%). Based on the relative abundance of the halogenated components in Blend A and exposure concentrations from 5-15% v/v, the only component that achieved a LOAEL for cardiac sensitization was HCFC-22. Therefore the egress time for Blend A could be based on the concentration of HCFC-22 concentration resulting from a Blend A exposure. This assumes that the chemicals act independently with respect to toxicity in the biological systems of interest. Table 13 provides the resulting component concentrations based on Blend A concentration. Since the HCFC-22 concentration reaches its LOAEL of 5% at a 6.1% concentration of Blend

A, the LOAEL for Blend A should be 6.1%. Referring to the HCFC-22 data in Table 10, the time required to achieve the cardiac sensitization target chemical concentration in blood is 5 minutes.

Table 13. Component Concentrations Resulting from Blend A.

Exposure Conc (v/v) of 100% Blend A	Resulting Conc (v/v) of HCFC-22	Resulting Conc (v/v) of HCFC-124	Resulting Conc (v/v) of HCFC-123
5	4.10	0.48	0.24
6	4.92	0.57	0.29
6.1	5.00	0.58	0.29
7	5.74	0.67	0.33
8	6.56	0.76	0.38
9	7.38	0.86	0.43
10	8.20	0.95	0.48
11	9.02	1.05	0.52
12	9.84	1.14	0.57
13	10.66	1.24	0.62
14	11.48	1.33	0.67
15	12.30	1.43	0.71

DISCUSSION

A simulation of the time course of chemical concentration in blood was used to estimate the time required to reach the blood concentration attained in the cardiac sensitization tests at the NOAEL. This approach was applied to a group of chemicals being evaluated for roles as replacements for Halon 1301 and other Halons being phased out of use. While this approach makes strides toward interfacing toxicity tests and their application in occupational and military operational settings, some caveats should be identified in order to properly apply the products of this approach.

The simulations of chemical concentrations in blood during an inhalation exposure were conducted using a physiologically based pharmacokinetic model. PBPK models have been used extensively to describe chemical fate in biological systems and as such have become substantial tools in health risk assessment applications. However, PBPK models have physiological and chemical data requirements, the quality of which play an important role in the utility of the model. For the most part, the physiological parameters required for a human or rat PBPK model are defined well enough to construct compartments for blood and the major organs. Examples of the physiological parameters are blood flows to the tissues, tissue volumes, ventilation rate and cardiac output. These physiological parameters define a particular biological system and are independent of the particular chemical of interest as long as the chemical does not produce a kinetically relevant change in the physiological processes. Chemical specific parameter values are

required for each chemical that is to be evaluated using the PBPK model. Examples of chemical specific parameters are tissue:blood partition coefficients and metabolic rate constants. These chemical specific parameter values are often lacking since they are not collected as part of the currently used toxicity test protocols commonly employed for risk assessment purposes. The chemicals used in this effort are examples of just such a situation. Cardiac sensitization levels were determined based on cardiac electrical activity, but lacked the partitioning and kinetic data required to construct a quantitative tool for extrapolating between species and exposure scenarios. Essentially no useable human partitioning or kinetic data were available for the chemicals of interest. In order to accomplish the simulation of chemical concentration in human blood during an inhalation exposure, kinetic and tissue partitioning data were collected in rats. The rat data were then mathematically scaled to humans and used in the simulations. One exception to the data deficit was human blood:air partition coefficients. The availability of human blood made these partition coefficient determinations practical. This is particularly important since the blood:air partition coefficient is the major determinant in the amount of chemical that gains access to the biological system during the inhalation exposure. As a consequence of the lack of human data, obviously the model could not be validated against actual human exposures. However, in terms of the application this may not be grounds to diminish the usefulness of this approach. Currently, the cardiac sensitization LOAEL determined in dogs is directly applied in setting allowable exposure limits for humans. This is allowed most likely because the cardiac sensitization test is considered extremely conservative.

A couple of points can be made based on the data in Tables 10-12. First, in terms of time required to reach the target chemical concentration in blood equivalent to that achieved at the NOAEL, some exposures will not produce the target chemical concentrations no matter how long the exposure continues. Second, exposure concentrations well above the NOAEL can take minutes to reach the target chemical concentration in blood. And third, exposure concentrations well below the LOAEL can reach target chemical concentrations in blood if the exposure continues long enough. These points may be useful in deciding on appropriate egress times based on the expected exposure concentrations.

The blood time course shown in Figure 1 demonstrates the importance of exposure time in the cardiac sensitization test. Since there are currently protocols that expose animals to the chemical via inhalation for 5, 10 and 30 minutes, the animals could be at very different levels relative to their steady-state chemical concentration in blood. If the animals are not at or near steady-state when the cardiac sensitization test is conducted, there is potential for error in assignment of exposure concentrations that reach cardiac sensitization thresholds.

The quantitative relationship between chemical time courses in blood and cardiac sensitization potential described in this work can be used to assess appropriate egress times for people exposed to inhalation of Halon replacement chemicals. The PBPK model simulations of chemical concentrations in blood during inhalation exposures showed that it

is possible to be exposed to concentrations above the NOAEL for some period of time without reaching the target blood concentration of chemical. Additionally, the importance of cardiac sensitization test exposure times for appropriate determination of LOAEL and NOAEL values was demonstrated. The use of a PBPK model to link exposure scenarios to biological effects represents an approach that could benefit regulators and decision makers working on Halon replacement activities. The benefit of this approach could be greatly enhanced if kinetic and partitioning data were routinely collected as part of the toxicity tests relevant to Halon replacement issues. Even with the current data limitations this approach adds a tool for making scientifically based decisions to ensure an appropriate balance between operational effectiveness and human safety.

REFERENCES

Andersen ME 1981. A Physiologically Based Toxicokinetic Description of the Metabolism of Inhaled Gases and Vapors at Steady State. Toxicology and Applied Pharmacology 60:509-526.

Clewell HJ III and Andersen, ME. 1985. Risk Assessment Extrapolations and Physiological Modeling. Toxicology and Industrial Health 1(4):111-131.

Conolly RB and Andersen, ME. 1991. Biologically Based Pharmacodynamic Models: Tools for Toxicological Research and Risk Assessment. Annu. Rev. Pharmacol. Toxicol. 31: 503-523.

Dankovic DA and Bailer AJ. 1993. The Impact of Exercise and Intersubject Variability on Dose Estimates for Dichloromethane Derived from a Physiologically Based Pharmacokinetic Model. Fundamental and Applied Toxicology 22: 20-25.

Gargas ML, Burgess RJ, Voisard DE, Cason GH and Andersen ME. 1989. Partition Coefficients of Low-Molecular-Weight Volatile Chemicals in Various Liquids and Tissues. Toxicology and Applied Pharmacology. 98: 87-99.

Leung HW. 1991. Development and Utilization of Physiologically Based Pharmacokinetic Models for Toxicological Applications. Journal of Toxicology and Environmental Health 32: 247-267.

Ramsey JC and Andersen ME. 1984. A Physiologically Based Sescription of the Inhalation Pharmackinetics of Styrene in Rats and Humans. Toxicology and Applied Pharmacology 73: 159-175.

Vinegar A, Williams RJ, Fisher JW and McDougal JN. 1994. Dose-Dependent Metabolism of 2.2-Dichloro-1,1,1-trifluoroethane: A Physiologically Based Pharmacokinetic Model in the Male Fischer 344 Rat. Toxicology and Applied Pharmacology 129: 103-113.